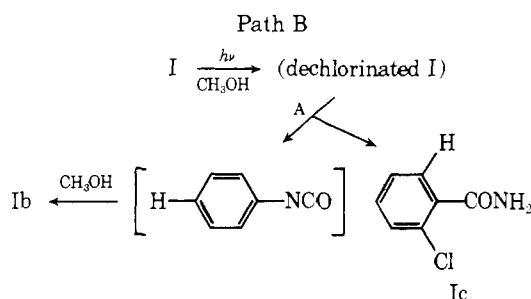


with ϵ in the order of 10^2 . The increased value observed for I and II implies an allowed transition involving the phenyl group α to the carbonyl. In aliphatic amides the photodissociative step involves type II fragmentation to the enol (Calvert and Pitts, 1966). Compounds I or II could presumably undergo a similar process. The result is then path A (Scheme I) which can occur without formation of "free radicals." Furthermore, conjugative effects imply that the excitation will occur at that carbonyl group. This type of an excited state has been described by Stenberg (Stenberg and Dutton, 1972). Absence of free radicals is justified in that in the photolysis of I in benzene, products Ia and Ib were predominant even though benzene is a very poor hydrogen donor.

Products from path B (Scheme II) have been observed with other chloro aromatic amides and dechlorination to form Ib and Ic has been substantiated (Elad *et al.*, 1965;

Scheme II



Reisch and Niemeyer, 1968). Methylcarbamates have also been observed to arise from isocyanates in methanol (Mazzochi and Rao, 1972).

We have found the dechlorination step to occur when pure Id was photolyzed in methanol. We have also found that Ia forms Id in the dark in >90% yield. Solutions of 2,6-dichlorobenzamide in methanol were found to be uv stable up to 60 hr of irradiation; dechlorination from the ortho position of I must therefore occur prior to C-N cleavage. No defluorination products from II were observed. This is in agreement with evidence of greater reactivity down the sequence F < Cl < Br < I. The slightly enhanced photodecomposition of I in acid or base supports the intermediacy of enol-like excited states or intermediates. Oxygen saturated solutions of I showed no rate decrease suggesting that the reaction does not proceed *via* a long-lived triplet excited state.

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Fenfluramine Residues in Chickens and Eggs

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The disappearance of fenfluramine, [*N*-ethyl- α -methyl-*m*-(trifluoromethyl)phenethylamine] hydrochloride, an anorexigenic agent, from chicken tissues and eggs was established. No detectable residue of fenfluramine or its deethylated metab-

olite (norfenfluramine) could be found, following administration of 300 g/ton of feed, after 6 days in the eggs and after 2 days in the tissues, following withdrawal of the drug.

Fenfluramine, [*N*-ethyl- α -methyl-*m*-(trifluoromethyl)phenethylamine] hydrochloride, has found extensive use as a very effective anorexigenic agent showing little or no CNS stimulant properties in humans and lower animals (Franko *et al.*, 1965). The present study was undertaken as part of an investigation to determine whether fenfluramine would be a useful agent for the control of weight in broiler breeders. Broiler breeder hens in contrast to layer breeders are selected and are genetically elegant to produce fat, fast gaining heavy birds. This body condition of obesity reduces egg production and longevity. By maintaining broiler breeders in a lean, trim condition through limitation of feed intake you obtain higher egg production and a longer productive life. This is not possible by simply limiting the feed allowed because birds eat litter, each other, and anything else available. In an unpublished part of this investigation (Gilbert, 1971) it had been shown that fenfluramine was effective in weight reduction, and did not give toxic effects nor affect egg production. The study reported here was undertaken to show the maxi-

mum concentrations of fenfluramine that may be found in tissues and eggs, and to determine the rate of disappearance of the drug following the feeding of an effective dose to chickens.

The metabolism of fenfluramine in lower animals and man has previously been reported (Duhault and Fenard, 1965; Beckett and Brookes, 1964; Bruce and Maynard, 1968). The main metabolic products are deethylated fenfluramine, α -methyl-*m*-(trifluoromethyl)phenethylamine (norfenfluramine), and *m*-trifluoromethylhippuric acid. Since norfenfluramine might be expected to show similar activity to fenfluramine, it was also determined in this study.

EXPERIMENTAL SECTION

Analytical Methods. The analytical method previously reported for determining urine concentrations (Bruce and Maynard, 1968) was adapted for use in this study. The gas chromatograph was a Barber-Colman with flame ionization detectors. The $\frac{1}{8}$ in. stainless steel column was 6 ft long with 10% Carbowax 20M and 5% KOH on Gas-Chrom Q and was operated at 120°. The injector and detector temperatures were 260°, and the nitrogen flow rate was 30 ml/min.

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Fenfluramine and norfenfluramine were extracted from tissues by the following procedures. A sample of tissue was homogenized with water in a blender, and the homogenate and washings of the blender were transferred to a volumetric flask, the contents diluted to the mark and mixed thoroughly, and an aliquot taken. The size of aliquot varied with the tissue (5 g, except for the kidney where 2 g was used). The next step, in the case of liver, fat, and skin, was to remove fat-soluble material from the samples. This was accomplished by adding 2 N HCl (approximately 2 ml) and then extracting with large (50 ml) volumes of ethyl ether repeatedly until the ether was colorless. All samples were then made alkaline with 2 N NaOH and the amines extracted with ether (20, 10, and 10 ml). The ether was dried through anhydrous Na₂SO₄ and concentrated to 500 μ l (200 μ l for kidney), and 5 μ l was injected into the gas chromatograph. Peak heights were compared with those of known amounts in ether. Blood was analyzed by a similar procedure using 5-ml aliquots.

Drug levels in eggs were determined by first mixing the egg white and yolk together. A 5-ml aliquot was diluted to 25 ml with water and 10 ml of methanol was added before alkalization with 1.0 ml of 2 N NaOH. The sample was extracted with ether and analyzed as described for tissues. When the yolk alone was analyzed, methylene chloride was used for extraction instead of ether.

Repeated extractions of whole eggs of a hen that had received 300 g/ton of feed were made in order to determine whether the extraction procedure was efficient. The first extract (20 ml of ether) contained 9.0 μ g of fenfluramine and 4.0 μ g of norfenfluramine. The second extract (10 ml) contained 0.5 μ g of fenfluramine and 0.3 μ g of norfenfluramine. Additional extractions (3 \times 10 ml) did not contain measurable amounts. Similar results were obtained with tissues and it was concluded that the extraction procedure was satisfactory.

Poultry Studies. Materials. A 22% premix of fenfluramine hydrochloride in dicalcium phosphate (Monsanto) was made and incorporated into Purina cage laying mash (300 g of fenfluramine HCl/ton of feed). Feed was mixed twice during the study. Samples of each were saved and analyzed.

Experimental. Thirty-six 22-week-old pullets (Rhode Island Red Cross) were assigned at random to individual laying cages having individual feed cups. Hens were fed unmedicated (basal) Purina cage laying mash for a 2-week conditioning period to adjust to the laboratory environment. Food consumption was determined for the group and egg production records for the individual birds were kept for this time. At the end of this period, the hens were weighed.

Medicated feed containing 300 g of fenfluramine HCl/ton was started on July 13, 1971. Individual birds were weighed and group food consumption was determined at the end of 13, 27, 49, and 69 days. Records of egg production on individual hens were kept and eggs were identified with treatment and date. Birds were fed unmedicated feed (basal) from day 70 until sacrificed. On day 69, the last day the hens were on medicated feed, 10 ml of whole blood was taken from the wing vein of three hens that had been fasted overnight. Then, the birds were euthanized, bled out, and examined grossly at necropsy. Samples of blood, meat (white and dark), skin, liver, kidney, and fat were frozen in Dry Ice and stored for future drug level determination. On each of 8 days of the withdrawal period, three additional birds were bled, sacrificed, and the tissues frozen in Dry Ice.

RESULTS AND DISCUSSION

Recoveries of fenfluramine and norfenfluramine added to control tissues were run on at least five samples of each tissue at a level of 10 ppm for standard deviations. The

Table I. Recovery of Fenfluramine from Eggs and Tissues following the Addition of Known Amounts

ppm		ppm	
Added	Found	Added	Found
Eggs		Skin	
0.04	0.04	10	9.9
0.08	0.08	10	9.0
0.08	0.08	10	9.7
0.12	0.12	20	20.2
0.16	0.18	30	29.1
0.20	0.22	S.D. at 10 = 0.41	
0.32	0.31	Liver	
S.D. at 0.16 = 0.02		0.20	0.18
Blood		1.00	0.96
10	9.6	10	9.7
10	9.5	10	9.6
10	10.0	10	10.0
20	19.3	20	19.6
30	28.3	30	30.6
S.D. at 10 = 0.21		S.D. at 10 = 0.17	
Eggs		Liver	
0.40	0.42	0.20	0.20
0.50	0.50	1.00	0.96
0.80	0.80	2.00	2.04
1.00	0.88	4.00	3.80
2.00	1.96	10.00	9.60
4.00	4.00	S.D. at 10 = 0.30	
S.D. at 1.00 = 0.19		Fat	
Muscle		0.20	0.18
0.20	0.20	1.00	0.92
1.00	1.00	2.00	1.92
2.00	1.92	4.00	4.08
4.00	4.00	10.00	10.40
10.00	9.80	S.D. at 10 = 0.63	
S.D. at 10 = 0.17		Muscle (white)	
Kidney		0.20	0.18
10	9.9	1.00	1.04
10	10.3	10	9.4
10	9.7	10	10.0
20	19.0	10	9.4
30	28.9	20	18.8
S.D. at 10 = 0.31		30	28.3
Muscle (dark)		S.D. at 10 = 0.29	
10	10.4	Fat	
10	10.2	0.20	0.19
10	9.8	1.00	0.94
20	19.2	10	10.2
30	28.5	10	9.7
S.D. at 10 = 0.40		10	9.7
		20	20.0
		30	28.4
		S.D. at 10 = 0.26	

results and standard deviations are presented in Table I and appear to be satisfactory for the present purposes. The method is sensitive to at least 0.04 ppm. Recoveries from control eggs are also presented.

Samples of tissues and eggs from hens used in a toxicity study were obtained and analyzed during some preliminary work. The tissues were taken after the hens, which

Table II. Determination of Fenfluramine Hydrochloride and Norfenfluramine Hydrochloride in Whole Eggs of Hens Fed 100 or 300 g of Fenfluramine HCl per Ton of Feed after 14 Days Feeding

Hen no.	Fenfluramine HCl, ppm	Norfenfluramine HCl, ppm
100 g/Ton		
1	0.65	0.50
4	0.33	0.36
16	0.27	0.50
26	0.94	0.34
34	1.10	0.65
300 g/Ton		
15A	1.07	0.75
22	1.85	0.90
25	1.02	0.36
25	2.38	
36	1.20	0.40
15B	1.34	

Table III. Results from the Determination of Fenfluramine HCl and Norfenfluramine HCl in Yolks and Whites of Eggs from Hens Being Fed 300 g of Fenfluramine per Ton of Feed, after 14 Days Feeding

Hen no.	Yolks		Whites	
	Fen-fluramine HCl, ppm	Norfen-fluramine HCl, ppm	Fen-fluramine HCl, ppm	Norfen-fluramine HCl, ppm
13	1.30	1.45	0.19	0.63
14	2.41	2.14	0.20	0.27
22	2.11	0.96	0.19	0.63
14	2.00	0.50	0.83	0.15
22	1.76	0.84	0.55	0.16
35	2.16	1.93	0.37	0.31

Table IV. Results from the Determination of Fenfluramine HCl and Norfenfluramine of Whole Eggs from Hens Receiving 300 g of Fenfluramine HCl per Ton of Feed; Mean of Six Eggs and Standard Deviation

Week no.	Fenfluramine HCl, mean ppm (\pm S.D.)	Norfenfluramine, mean ppm (\pm S.D.)
1	0.92 (0.60)	0 ^a
2	1.20 (0.55)	1.13 (0.59)
3	1.23 (0.60)	1.38 (0.40)
4	1.96 (0.39)	2.42 (0.39)
5	2.14 (0.83)	2.67 (0.92)
6	1.72 (0.60)	0.93 (0.52)
7	3.20 (0.80)	1.24 (0.82)
8	1.68 (0.59)	0.45 (0.20)

^a Represents less than 0.04 ppm.

had received 100 or 300 g/ton of feed, had been removed from the diet for 28 days, and analyses failed to show the presence of fenfluramine or its metabolite. Eggs were taken while they were receiving the drug. The results of the analysis of these eggs are shown in Table II. The average concentration of fenfluramine hydrochloride found at the 100 g/ton level was 0.66 ppm while that at 300 g/ton was 1.77 ppm, indicating a relationship between dose and residue concentrations.

The whites and yolks of six of these eggs were separated

Table V. Eggs from Hen No. 36 Taken at Intervals While Being Fed 300 g/Ton of Fenfluramine HCl

Day	Fenfluramine, ppm	Norfenfluramine, ppm
1	0 ^a	0 ^a
7	0	0
11	1.04	0.28
15	1.26	0.61
17	1.26	0.28
20	1.73	0.50
21	2.46	0.80
24	1.98	0.28
25	2.69	0.40
27	3.89	4.00
28	2.46	1.93
29	1.09	0.59
30	1.66	0.96
31	1.04	0.46
32	2.28	0.91
34	1.07	0.32
35	1.13	0.63
36	1.80	1.53
37	0.92	0.35
39	1.30	0.56
41	2.54	0.87
43	2.13	0.65

^a Represents less than 0.04 ppm.

Table VI. Results from the Analyses of Eggs from Hens That Received 300 g of Fenfluramine HCl per Ton of Feed for 69 Days and Then Received a Diet Containing No Fenfluramine^a

Days off fenfluramine	Hen no.	Fenfluramine, ppm	Norfenfluramine, ppm
1	9	2.25	0.55
1	14	1.82	0.30
1	29	1.16	0.18
2	4	2.16	0.32
2	7	1.76	0.61
2	25	2.50	1.23
3	17	1.39	0 ^b
3	18	0.88	0
4	7	1.18	0
4	35	1.11	0
5	15	1.58	0
5	20	0.75	0
6	18	0 ^b	0
6	24	0	0
6	7	Trace	0
6	9	Trace	0
6	10	0	0

^a Analysis of samples for days 7 and 8 showed less than 0.04 ppm of fenfluramine and norfenfluramine present. ^b Represents less than 0.04 ppm.

and analyzed in order to investigate the distribution of fenfluramine and its metabolite. The results, shown in Table III, indicate that a larger amount occurs in the yolk, as would be expected from its higher fatty material content.

The above toxicology study revealed no pharmacological

or toxicological symptoms and all the birds remained healthy throughout the study. Feed consumption was significantly reduced at the 300 g/ton level and the birds in this group ended the medication period gaining 60% as much weight as the control group. There were no discernible differences in the quality of the eggs or the egg shell.

Following the toxicology study, the feeding study described in the Experimental Section was carried out. In order to obtain some indication as to when a plateau in tissue level was reached, six eggs were randomly taken at weekly intervals and analyzed. The results from these analyses are shown in Table IV and, although there is a great variation between egg concentrations for each week, a plateau appears to have been reached by at least the fourth or fifth week. The variations in concentrations were great enough to warrant a study of the variations within the eggs of one hen. The results of these analyses are shown in Table V and indicate variations from 0.9 to 3.9 ppm for fenfluramine and 0.28 to 4.0 ppm for norfenfluramine. The source of these differences is not immediately apparent but may reflect daily variations in food consumption.

After the hens had been on the diet containing fenfluramine for 69 days, the diet was changed to one containing no fenfluramine. Beginning with the day the diet was changed and each day thereafter, three randomly selected hens were sacrificed. Eggs continued to be collected from the remaining hens and the rate of disappearance of fen-

fluramine was determined in these eggs. The results, shown in Table VI, indicate that at the sixth day after withdrawal of the drug no fenfluramine or its metabolite could be found.

Tissues and blood were taken for analysis when the birds were sacrificed and were analyzed at each interval until no further residue could be detected in the tissue. The results indicate that no detectable residue was present after the second day off of the medication. None could be detected in blood or muscle on the day of withdrawal of fenfluramine. (None could be detected in any of the tissues on the second day of withdrawal.) Residues persisted for 1 day longer in the kidney than in any of the other tissues including fat. The rate of disappearance would be expected to be slower from the eggs than from the tissues since these are formed several days prior to being laid.

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Synthesis and Herbicidal Activity of Fluorinated *N*-Phenylalkanesulfonamides

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Four general techniques have been developed for the preparation of a series of *N*-phenylalkanesulfonamides, fluorinated in the (alkanesulfonyl)-amino moiety. Herbicidal and plant growth regulatory activities were exhibited over a wide range of structure type. Preemergence herbicidal activity was greatest with halogen and sulfur aryl-substituted 1,1,1-trifluoro-*N*-phenylmethanesulfonamides. Crop selectivity with high herbicidal activity was apparent for 2-methylthio, 4-methylsulfanyl, 2,4-dichloro, and 2,4-dibromo aryl-sub-

stituted 1,1,1-trifluoro-*N*-phenylmethanesulfonamides. Postemergence herbicidal activity paralleled preemergence activity but was generally less marked. High herbicidal activity in the 1,1,1-trifluoro-*N*-phenylmethanesulfonamides generally was accompanied by high acidity and lipophilicity. Computer correlations of herbicidal activity with structure indicated that lipophilic effects are more important for herbicidal activity with the 4-substituted than with the 3-substituted 1,1,1-trifluoro-*N*-phenylmethanesulfonamides.

Sulfonamides have found extensive medicinal applications since the discovery of Prontosil in 1932. Scores of sulfonamides have been synthesized and many found effective for the treatment of bacterial infections. These early drugs were essentially all benzenesulfonamides. Alkanesulfonamides have found little use in the medicinal area. Generally, alkanesulfonamides have been used as substituents to slightly modify the biological activity of compounds found active previously.

The first reported synthesis of *N*-phenylalkanesulfonamides, fluorinated in the (alkanesulfonyl)amino moiety (perfluoro-*N*-phenyloctanesulfonamide and 1,1,1-trifluoro-*N*-phenylmethanesulfonamide), was from these laboratories (Brice and Trott, 1956). More recently, 1-fluoro- and 1,1-difluoro-*N*-phenylmethanesulfonamides were reported

(Farrar, 1960). In 1970 we published preliminary reports of potent herbicidal (Trepka *et al.*, 1970) and antiinflammatory (Harrington *et al.*, 1970) activity for a number of these fluorinated *N*-phenylalkanesulfonamides. Biological activity is largely due to the presence of the fluorinated (alkanesulfonyl)amino group and we have found it to be highly dependent upon the degree of fluorination. However, activity can be modified by substitution in the aromatic portion of the structure. We now wish to describe the synthetic procedures used to prepare these compounds and to relate other details of their biological properties. Throughout this paper the term fluorinated *N*-phenylalkanesulfonamides refers to fluorination in the (alkanesulfonyl)-amino group.

RESULTS

Synthesis. Representative fluorinated *N*-phenylalkanesulfonamides and references to their methods of prepara-

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